federal register

WEDNESDAY, DECEMBER 7, 1977
PART IV

ENVIRONMENTAL PROTECTION AGENCY

REBUTTAL PRESUMPTION AGAINST REGISTRATION AND CONTINUED REGISTRATION OF PESTICIDE PRODUCTS CONTAINING THIOPHANATE-METHYL

[6560–01]

ENVIRONMENTAL PROTECTION AGENCY

[OPP–30000/24; FRL 822–3]

PESTICIDE PROGRAMS

Rebuttable Presumption Against Registration and Continued Registration of Pesticide Products Containing Thiophanate-Methyl

AGENCY: Office of Pesticide Programs, Environmental Protection Agency (EPA).

ACTION: Notice of rebuttable presumption.

SUMMARY: Thiophanate-methyl has been found to exceed certain risk criteria set forth in 40 CFR 162.11. This notice requests registrants and other interested persons to submit rebuttals and other information on the presumption and to submit any other data on the risks and benefits of this pesticide chemical. This notice is the first of several which will give public notification of the Agency's progress in reviewing this chemical.

DATES: Rebuttal evidence and other information must be recieved on or before January 24, 1978.

ADDRESS MATERIAL TO: Federal Register Section, Technical Services Division (WH–569), Office of Pesticide Programs, EPA, room 401, East Tower, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT:

Esther Saito, Office of Special Pesticide Reviews, Office of Pesticide Programs (WH–566), room 447, East Tower, EPA 202–755–8050.

SUPPLEMENTARY INFORMATION: The Deputy Assistant Administrator, Office of Pesticide Programs, EPA, has determined that a rebuttable presumption exists against registration and continued registration of all pesticide products containing thiophanate-methyl.[1]

I. Regulatory Provisions

A. *General.* Title 40, Part 162.11, of the Code of Federal Regulations for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) as amended (86 Stat. 973, 89 Stat. 751, 7 U.S.C. 136 *et seq.*), provides that a rebuttable presumption against registration shall arise if the Agency determines that a pesticide meets or exceeds any of the risk criteria relating to acute and chronic toxic effects set forth in § 162.11(a)(3). If it is determined that such a rebuttable presumption has arisen, the regulations require that the registrant be notified by certified mail and afforded an opportunity to submit evidence in rebuttal of the presumption. In addition, the Agency has determined that the public should also be given notice of the bases for the presumption to provide an opportunity for comment and to solicit additional information relevant to the presumption.

A notice of rebuttable presumption against registration is issued when the evidence related to risk meets the criteria set forth in § 162.11(a)(3). It is emphasized that a notice of rebuttable presumption against registration and continued registration of a pesticide is not a notice of intent to cancel the registration of a pesticide, and may or may not lead to cancellation. The notice of intent to cancel is issued only if, after careful consideration of both the risks and benefits, it is determined that the pesticide may generally cause unreasonable adverse effects to the environment.

Accordingly, all registrants and applicants for registration are invited pursuant to 40 CFR 162.11(a)(4) to submit evidence in rebuttal of the presumptions listed in Part II of this notice. Registrants and other interested parties may also submit for consideration data on benefits which they believe would justify registration or continued registration. In addition, any registrant may petition the Agency to voluntarily cancel a current registration pursuant to Section 6(a)(1) of FIFRA.

B. *Rebuttal Criteria.* Section 162.11 (a)(4) provides that a registrant may rebut the presumption by sustaining the burden of proving:

(1) In the case of a pesticide presumed against pursuant to the acute toxicity or lack of emergency treatment criteria, "that when considered with the formulation, packaging, method of use, and proposed restrictions on and directions for use and widespread and commonly recognized practices of use, the anticipated exposure to an applicator or user and to local, regional, or national populations of nontarget organisms is not likely to result in any significant acute adverse effects" (40 CFR 162.11(a)(4)(i));

(2) In the case of a pesticide presumed against pursuant to the chronic toxicity criteria, "that when considered with proposed restrictions on use and widespread and commonly recognized practices of use, the pesticide will not concentrate, persist or accrue to levels in man or the environment likely to result in any significant chronic adverse effects" (40 CFR 162.11(a)(4)(ii)); or

(3) In either case, that "the determination by the Agency that the pesticide meets or exceeds any of the criteria for risk was in error" (40 CFR 162.11(a)(4)(iii)).

C. *Benefits Information.* In addition to submitting evidence to rebut the presumption of risk, Section 162.11(a)(5)(iii) provides that a registrant "may submit evidence as to whether the economic, social and environmental benefits of the use of the pesticide subject to the presumption outweigh the risk of use." If the risk presumptions are not rebutted, the benefit evidence submitted by the registrant,[2] applicants, and other interested persons will be considered by the Administrator in determining the appropriate regulatory action. Specifically, § 162.11(a)(5)(iii) provides that if the "benefits appear to outweigh the risks," the Administrator may issue a notice of intent to hold a hearing pursuant to Section 6(b)(2) of FIFRA rather than a notice of intent to cancel or deny registration pursuant to Section 3(c)(6) of FIFRA. Alternatively, if the "benefits do not appear to outweigh the risks, the Administrator shall issue a notice pursuant to Section 3(c)(6) or Section 6(b)(1) of the Act, as appropriate." Moreover, if at any time the Administrator determines that a pesticide poses an "imminent hazard" to humans or the environment, a notice of suspension may be issued pursuant to Section 6(c) of the Act.

Stated below are the Section 162.11 (a)(3) risk criteria which the Agency has found to have been met or exceeded by registrations and applications for registration of pesticide products containing thiophanate-methyl. The Agency's basis for concluding that these risk criteria have been met or exceeded is set out in "Thiophanate-methyl: Position Document 1," which follows. Copies of attachments to the Position Document which are not published with this notice are available for public inspection in the Office of Special Pesticide Reviews. Information protected from disclosure pursuant to FIFRA Section 10 cannot be provided. Specific inquiries concerning the Position Document, as well as requests for access to these files, should be directed to Project Manager Mrs. Esther Saito, Office of Special Pesticide Reviews (WH–566), EPA, Room 447, East Tower, 401 M St. SW., Washington, D.C. 20460, 202–755–8050.

---

[1] A position of document, containing an appendix of references, background information, and other material pertinent to the issuance of this notice, has been prepared by the Agency Working Group on thiophanate-methyl and is also published with this notice.

[2] Registrants or other interested persons who desire to submit benefit information should consider submitting information on the following subjects, along with any other relevant information they desire to submit:

1. Identification of the major uses of the pesticide, including estimated quantities used by crop or other application.
2. Identification of the minor uses of the pesticide, including estimated quantities used by category such as lawn and garden uses and household uses.
3. Identification of registered alternative products for the uses set forth in (1) and (2) above, including an estimate of their availability.
4. Determination of the change in costs to the user of providing equivalent pesticide treatment with any available substitute products.
5. Assessment of regulation impact upon user productivity (e.g., yield per acre and/or total output) from using available substitute pesticides or from using no other pesticides.
6. If the impacts upon either user costs or productivity are significant, a qualitative assessment of the regulation's impact on production of major agricultural commodities and retail food prices of such commodities.

II. Presumptions

A. *Mutagenicity.* 40 CFR 162.11(a)(3)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide "* * * (i)nduces oncogenic effects, as determined by multitest evidence."

On the basis of scientific studies and information summarized in the Position Document, the Agency has concluded that this risk index has been exceeded by all registrations and applications for registration of pesticide products containing thiophanate-methyl, and that a rebuttable presumption against new or continued registration of such products has therefore arisen.

B. *Population Reductions in Non-target Organisms.* 40 CFR 162.11(a)(3)(ii)(C) provides that a rebuttable presumption shall arise if a pesticide "(c)an reasonably be anticipated to result in significant local, regional, or national population reductions in nontarget organisms * * *"

On the basis of scientific studies and information summarized in the Position Document, the Agency has concluded that the risk index for population reductions in nontarget organisms has been exceeded by registrations and applications for registration of pesticide products containing thiophanate-methyl which are for outdoor use, and that a rebuttable presumption against new or continued registration of such products has therefore arisen.

III. Grounds for Pesticide Review in Addition to Rebuttable Presumption Criteria

As discussed in more detail in the attached Position Document, methyl 2-benzimidazole carbamate (MBC) has the potential of reacting with nitrites to form N-nitroso compounds. Some N-nitroso compounds are known to possess oncogenic properties. The data and analyses available at this time with respect to the potential formation of oncogenic compounds are not sufficient to warrant the issuance of a rebuttable presumption. The Agency specifically solicits further evidence bearing on the likelihood and significance of such reaction. Thiophanate-methyl is fetotoxic at high levels and requires additional teratogenic test. The Agency specifically solicits further data on human exposure. All comments and information received with respect to these potential reactions, including analysis thereof, may serve as a basis for a final decision as to the registrability of thiophanate-methyl pesticides (40 CFR 162.11(a)(6)).

IV. Registrations and Products Subject to the Notice

All registrants and applicants for registration listed below are being notified by certified mail of the rebuttable presumption existing against registration and continued registration of their products.

The registrants and applicants for registration shall have until January 24, 1978, to submit evidence in rebuttal of the presumption. However, the Administrator may, for good cause shown, grant an additional 60 days during which such evidence may be submitted. Notice of such an extension, if granted, will appear in the Federal Register.

A registrant or applicant for registration may, if it desires, assert a business confidentiality claim covering part or all of the information submitted in rebuttal. The registrant or applicant may assert the claim by placing on or attaching to the information a cover sheet, stamped or typed legend, or other suitable form of notice employing language such as as "trade secret," "proprietary," or "company confidential." Allegedly confidential portions of otherwise nonconfidential documents should be clearly marked.

If a confidentiality claim is asserted, the information covered by the claim will be disclosed by EPA only to the extent and by means of the procedures set forth in 40 CFR 2, Subpart B (41 FR 36906, September 1, 1976). If no confidentiality claim accompanies the information at the time it is received by EPA, EPA will place the information in the public comment file where it will be available for public inspection.

If a registrant or applicant does assert a confidentiality claim for some, but not all, of the information submitted to EPA in rebuttal, the registrant or applicant should furnish two copies of the information to EPA. The first copy should contain all of the information submitted in rebuttal with information claimed as confidential clearly identified. The second copy should be identical to the first except that all information claimed as confidential should be deleted. The second copy will be placed in the public comment file. The first copy will be treated in accordance with the procedures set out above.

V. Duty to Submit Information on Adverse Effects

Registrants are required by law to submit to EPA any additional information regarding any adverse effects on man or the environment which comes to a registrant's attention at any time, pursuant to Section 6(a)(2) of FIFRA and 40 CFR 162.8(d). If any registrant of Thiophanate-methyl products has any published or unpublished information, studies, reports, analyses, or reanalyses regarding any adverse effects in animal species or humans, residues, and claimed or verified accidents to humans, domestic animals, or wildlife, which *have not* been previously submitted to EPA, the material must be submitted immediately. When responding to this notice, each registrant shall submit a written certification to the Agency that all information regarding any adverse effects known to the registrant has been submitted. In addition, the registrants should notify EPA of any studies currently in progress, including the purpose of the study, the protocol, the approximate completion date, and a summary of all results observed to date.

VI. Public Comments

During the time allowed for submission of rebuttal evidence, specific comments on the presumptions set forth in this notice and on the material contained in the Position Document are solicited from the public. In particular, any documented episodes of adverse effects to humans, domestic animals, or wildlife, and information as to any laboratory studies in progress or completed, are requested to be submitted to EPA as soon as possible. Specifically, information on the fate and effects of Thiophanate-methyl, its impurities, metabolites, and degradation products on flora and fauna, particularly animals with metabolism similar to that in humans, is solicited. Similarly, any studies or comments on the benefits from the use of Thiophanate-methyl are requested to be submitted. All comments and information received, as well as any other relevant information and analysis thereof, which come to the attention of the Agency may serve as a basis for final determination pursuant to § 162.11(a)(5).

All comments and information should be sent to:

Federal Register Section, Technical Services Division (WH-569), room 401 East Tower, 401 M Street SW., Washington, D.C. 20460.

Three copies of the comments or information should be submitted to facilitate the work of the Agency and others interested in inspecting them. The comments and information should bear the identifying notation "OPP-30000/24." Comments and information received within the specified time limit shall be considered before it is determined whether a notice shall be issued in accordance with 40 CFR 162.11(a)(5)(ii).

Comments received after the specified time period will be considered only to the extent feasible, consistent with the time limits imposed by 40 CFR 162.11(a)(5)(ii). All written comments and information filed pursuant to this notice will be available for public inspection in the office of the Federal Register Section from 8:30 a.m. to 4 p.m. during normal working days.

Interested persons are encouraged to take advantage of the opportunity to inspect Agency files during normal working hours since 1) all of the information received may serve as a basis for final determination pursuant to 162.11(a)(5) and 2) the Agency will not generally publish a summary of information received in the Federal Register at the close of the rebuttal period.

Your cooperation is solicited in identifying any errors or emissions which may have been made in the following computer listings. Corrections to the listings may not necessarily be published in the Federal Register, but rather handled by mail with affected parties. Omissions will be corrected by notice in the Federal Register.

Dated: November 23, 1977.

Edwin L. Johnson,
Deputy Assistant Administrator for Pesticide Programs.

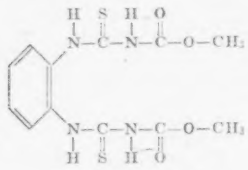
THIOPHANATE-METHYLS POSITION

DOCUMENT 1

THIOPHANATE-METHYL WORKING GROUP; ESTHER SAITO, PROJECT MANAGER, OFFICE OF SPECIAL PESTICIDE REVIEWS, U.S. ENVIRONMENTAL PROTECTION AGENCY

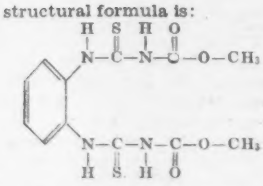
I. BACKGROUND

A. *Chemistry.*—1. *General Chemistry.* Thiophanate-methyl is the common name for the chemical 1,2-*a*-(3-methoxycarbonyl-2-thioureido) benzene. The accepted chemical name used on pesticide labels is dimethyl [(1,2-phenylene) bis(iminocarbonothioyl)] bis[carbamate]; it is sold under the the names Topsin M®, Cercobin M® and Thiophanate M. Thiophanate-methyl has the molecular formula $C_{12}H_{14}N_4O_4S_2$ and a molecular weight of 342.



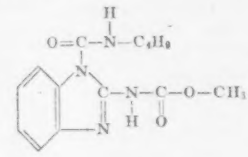
Thiophanate-methyl

The structural formula is:

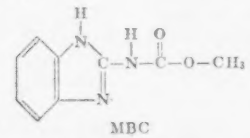


Thiophanate-methyl, a colorless crystalline solid melts at 168°C with decomposition. Thiophanate-methyl is slightly soluble in n-hexane, hardly soluble in water and sparingly soluble in most organic solvents. The compound is stable in acidic solutions, has a slight but measureable formation of methyl 2-benzimidazole carbamate (MBC) at pH7, and is unstable in alkaline solution.

Thiophanate-methyl and benomyl both metabolize to MBC (1,2).



Benomyl



MBC

MBC is a powerful fungicide that is generally regarded as the actual fungitoxic principle of benomyl (1). Vonk and Sipesteijn found a correlation between the formation of MBC and the fungitoxic activity of thiophanate-methyl (2). Thiophanate-methyl was completely converted to MBC in 0.066 M phosphate buffer, pH7, at 70°C in 26 hours (2).

2. *Residue Chemistry.*—a. *Soil.* In moist soil thiophanate-methyl was degraded rapidly: 80 to 90 percent had disappeared from Towner sand and Fargo clay soils five days after application (3). Thirty days after application of thiophanate-methyl to air-dried soil 10 to 20 percent thiophanate-methyl could be detected. The principal metabolite found in the soils was MBC. (3)

b. *Animals.* Noguchi and coworkers (3) and Fujino and coworkers (5), cited in the World Health Organization Technical Report Series (1974), reported that feeding ^{14}C– or ^{35}S– labeled thiophanate-methyl to rats, mice, and dogs showed 80 to 100 percent recovery in feces and urine within 96 hours. MBC has been identified as the major metabolite in both mice and dogs in studies submitted to EPA by Noguchi and coworkers (33).

Fujino and coworkers report unmetabolized thiophanate-methyl as the major part of the fecal excretion. The mnior part consisted of 4-hydroxy-thiophanate-methyl (4–OH–TM) and dimethyl-4.4'-O-phenylenebisallophanate (FH-432). MBC and 5-hydroxy-MBC (5-OH-MBC) were observed but the authors questioned if they were metobolites or were produced during the analytical procedures (5).

Kosaka and co-workers, cited in the World Health Organization Technical Report Series (1976), reported that 5-hydroxy methyl benzimidazole was the main metabolite in the urine of female rats, which had been administered ^{14}C-labelled thiophanate-methyl. Thiophanate-methyl, 5-hydroxy methyl benzimidazole, 4-hydroxy-dimethyl-4,4'-O-phenylene bis-allophanate were identified as metabolites in the feces (6).

c. *Plants.* Thiophanate-methyl was converted to MBC after uptake through roots and after foliar treatment of French bean seedlings (4) Buchenauer and coworkers (7) found that the transformation is to a great extent catalyzed by light in addition to requiring water. Thiophanate-methyl residues in cotton leaves were transformed to MBC; after four days in sunlight 42 percent were transformed as opposed to 6 percent when the plants were kept in dim light.

B. *Uses and Production.* Thiophanate-methyl was first registered for use as a fungicide in Japan in May 1971. Great Britain granted provisional clearance for a number of preharvest treatments on food crops and ornamentals and post-harvest dipping of apples in 1973 (8). Thiophanate-methyl is only registered for use on turf and ornamentals in the U.S.A.

Pennwalt is the only registered producer of technical grade thiophanate-methyl in the United States. Under Section 7(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) manufacturers and formulators are required to submit information on production, sales, and distribution. Under Section 10, this information is considered confidential and cannot be released to the public, but it is made available to the Administrator in a confidential appendix to this report (9).

II. REGULATORY HISTORY

The first registration for a product containing thiophanate-methyl was granted January 16, 1973, to Pennwalt for technical grade product (EPA Registration Number 4581-280). In July and August 1973, three companies registered products containing 50 to 70 percent thiophanate-methyl and formulated as wettable powders for use on turf. A wettable powder containing 1.15 percent thiophanate-methyl was registered for use on turf in February 1974. A product which contains 25 percent thiophanate methyl and 15 percent 5-ethoxy-3-(trichloromethyl)-1,2,4-thiadizole was registered for use on flowers and ornamentals in July 1974.

Tolerances were established, under 40 CFR Section 180.371 for residues on bananas (2 ppm of which only 0.2 ppm may be present in the pulp) on February 3, 1977; tolerances for residues on stone fruits (15 ppm) and strawberries (5 ppm) were added on March 17, 1977.

Although no products containing thiophanate-methyl are registered for use on food crops, an application is being reviewed for use on stone fruits and strawberries.

III. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

40 CFR 162.11 (a)(3) provides that a rebuttable presumption shall arise if a pesticide's ingredients, metabolites or degradation products meet or exceed (i) acute toxicity risk criteria relating to hazards to humans, domestic animals, or wildlife, or (ii) chronic toxicity risk criteria relating to humans and to population reductions in non-target organisms or fatality to members of endangered species.

A. *Chronic Toxicity.*—1. *Mutagenic Effects in Multitest Systems.* Section 162.11(a)(3)(ii)(A) provides that a rebuttal presumption shall arise if a pesticide's ingredients, metabolites, or degradation products induces mutagenic effects, as determined by multitest evidence.

Studies in plants (4, 7) animals (33) and soil (3) have shown that thiophanate-methyl is metabolized to MBC. MBC has been shown to produce somatic chromosomal abnormalities and point (gene) mutations in microbial and mammalian test systems. Further evidence of the mutagenic effects of thiophanate-methyl and MBC has been obtained in studies of plants. MBC has also been shown to reach gonadal tissues in mammals with physiological effects; hence it has the potential of interacting with genetic material.

a. *Chromosomal Effects.*—i. *Mammalian Cells in Culture:* MBC has been shown to cause mitotic delay (10), a low incidence of chromosomal breakage (10), and multinucleation (10, 11) in human, mouse, and hamster cells lines.

ii. *Mammalian Tests in Vivo.* Metaphase arrest and micronuclei formation occurred in bone marrow cells of rats treated with MBC; in addition there was a low frequency of chromosomal breakage and formation of anaphase bridges (10).

Seiler (1976) found that MBC produced dose-related mutagenic effects in the micronucleus test in mice. In addition, lagging choromosomes, anaphase bridges, unequally distributed chromosomes, and tripolar anaphases appeared in mitotic bone marrow cells of treated animals; none of these effects were noted in control cells (12). The author concluded that the main action of MBC was the inhibition of the mitotic spindle, which may predispose to nondisjunctional errors. The finding of anaphase bridges indicates that MBC can break chromosomes.

On the other hand thiophanate-methyl administered intraperitoneally (dosage range from 8 to 500 mg/kg) did not increase the frequency of dominant lethal mutations in ICR-strain mice (13). Abnormal chromosome configuration were not observed in bone marrow or spermatogonial cells of Wistar strain albino male rats treated daily for 5 days with thiophanate-methyl by intraperitoneal injection (62.5 to 1000 mg/kg) (13).

iii. *Fungi and Molds.* MBC interfered with normal nuclear division in *Saccharomyces cerevesiae, Ustilago maydis* (12), *Botrytis cineara* (13), and *Aspergillus nidulans* (14). Interference with cell division may predispose to chromosomal nondisjunction.

b. *Point Mutations.* i. *Bacteria.* Two studies have reported that MBC and other benzimidazoles induce base-substitution mutations as detected by the Ames test without metabolic activation. *Salmonella typhimurium* strains *his* G46, TA1530, and TA1535 were used in the tests. Forward mutations were induced in *Salmonella* strain LT–2 by MBC; reverse mutations were induced in *Escherichia coli* strain WP2 uvrA which is excision deficient but not in strain WP2, which is excision proficient (17, 18). Mutations appear to result from the incorporation of benzimidazoles into DNA in place of purine bases (19); it has been hypothesized that mutation occurs when the abnormal base is recognized by the cell but the defect is not repaired correctly (18). One study indicates that MBC does produce mutations in the *Salmonella typhimurium* test without metabolic activation or in the rodent host-mediated assay (20).

c. *Other Studies Bearing upon Mutagenicity.* Thiophanate-methyl, MBC, and other benzimidazole fungicides induced genetic segregation in a diploid strain of *Aspergillus nidulans* which was heterozygous for sporecolor markers and nutritional mutants (21).

Styles and Garner report that repeated oral doses of MBC produced toxic effects in rat testes showing that this compound can affect the primary reproductive tissues (10).

On the basis of the multitest studies, the Working Group concludes that MBC is mutagenic and recommends that a rebuttable presumption against all pesticide products containing thiophanate-methyl be issued.

2. *Effects on Nontarget Organisms: Reduction in Populations of Earthworms.* 40 CFR 162.11(a)(3)(ii)(C) provides that a rebuttable presumption shall arise if a pesticide's ingredients, metabolites, or regradation products can reasonably be anticipated to result in significant local, regional, or national population reductions in nontarget organisms.

The Agency staff has evaluated the methodology, protocol, and conclusions of several studies that indicate that thiophanate-methyl is highly toxic to earthworms. In studies by Stringer and Wright (22) earthworm populations were "virtually eliminated" in apple orchard plots sprayed with thiophanate-methyl. In addition, thiophanate-methyl was repellent to earthworms, apparently because it made food materials unpalatable to them. The spraying of thiophanate-methyl in orchards reduced not only the number and biomass of all earthworm species combined, but also that of each individual species (23).

Stringer and Lyons stated that earthworms are generally regarded as beneficial animals in maintaining soil fertility, but noted that it has not been rigorously proven that they are essential (23). Hopp claims that earthworm activity is not one of the three basic requirements for plant growth but is a factor which can be used to correct deficiencies in soil fertility (24). Thus, the Working Group is unable to adequately evaluate the environmental, agricultural, and economic significance of these population reductions. Comment is, therefore, especially solicited on the relevance, impact, and long-term significance of such local population reductions.

The Working Group recognizes that many other factors contribute to the size of earthworm populations, including soil composition, moisture, temperature, cultivation practices, and the use of other pesticides. Furthermore, it appears that the adverse effects on earthworms are generally limited to areas of application and do not extend significantly to adjacent areas. That is, the effects appear to be confined largely to privately owned land, the owners of which can be made aware of the likely effects on earthworms. Nonetheless, it is clear that the use of thiophanatemethyl according to current label directions can reasonably be expected to result in significant local reductions of earthworm populations. Accordingly, the Working Group concludes that a rebuttable presumption has arisen against pesticide products containing thiophanate-methyl which are registered for outdoor use.

IV. Other Relevant Adverse Effects

A. *Potential Formation of N-Nitroso Compounds.* Many chemicals can react with nitrites to form N-nitroso compounds (25) which as a class are recognized as animal carcinogens and mutagens (26).

Two papers (27, 28) dealing with the possible formation of N-nitroso MBC and induction of lymphosarcomas were reviewed. Both papers reported that neither MBC nor sodium nitrite alone produced tumors; tumors did develop in Swiss mice given large amounts of sodium nitrite (0.05 to 0.5 percent in drinking water) and administered MBC by gavage.

The fact that lymphosarcomas form in Swiss mice treated with MBC and nitrite but not in mice treated with MBC alone suggests that MBC and nitrite interact to create a stress that results in tumor production (27). Furthermore, offspring of mice treated with MBC and nitrite during gestation developed tumors, whereas offspring of animals treated with MBC alone did not (28).

Evaluations of these studies state that the data do not provide evidence for in vivo production of N-nitroso MBC (29,30). Additional data necessary in order to evaluate the hazards of N-nitroso MBC would include kinetic studies and information on the isolation of an N-nitroso MBC derivative formed in vivo, and rate of formation of N-nitroso MBC in the soil and rate of uptake into plants (30).

Although there is no evidence at present that N-nitroso compounds are formed from MBC, nitrosation can take place on either of the two nitrogen sites. Formation of N-nitroso compounds might occur after the pesticide is applied if nitrites are present. Such formation is therefore possible in soil, water, air, plants, and animals, including man (30).

The potential formation of N-nitroso MBC is a matter of concern. The Working Group recommends that the Agency solicit further information on the formation of N-nitroso compounds from MBC, the conditions necessary for formation of such compounds, and their potential as carcinogenic and mutagenic agents.

B. *Teratogenic and reproductive effects.* The Working Group has considered a paper on the teratogenic effects of thiophanate-methyl, which has been reviewed by Battelle Memorial Laboratories (31). Makita and co-workers administered thiophanate-methyl by gavage to ICR mice (dosage levels from 40 to 1,000 mg/kg) from day 1 to day 15 of gestation (13). The only observed malformation was cleft palate which occurred with the same incidence in the control and experimental animals. The highest dosage level (1,000 mg/kg) resulted in a slight reduction in the number of living fetuses with the no-effect level (500 mg/kg) appearing to represent an adequate margin of safety. However, the study should be considered inconclusive for determining teratogenic effects because apparently brain, spinal cord, heart, and urogential organs were not examined (31).

In a 3-generation reproductive study of the effect of thiophanate-methyl on the rat, Palmer and co-workers administered thiophanate methyl in the diet to CD strain (Charles River) rats (70–80 g) at levels of 0, 40, 160, and

In a 3-generation reproductive study of the effect of thiophante-methyl on the rat, Palmer and co-workers administered thiophanate-methyl in the diet to CD strain (Charles River) rats (70–80 g) at levels of 0, 40, 160, and 640 ppm. At the 640 ppm level a slightly lower litter size from birth to weaning consistently occurred in all generation and there was a tendency for lower litter weight from birth through lactation to weaning. Skeletal variations, which did not appear in the control animals, were observed at three experimental dosage levels, although the anomalies were not dose dependent (32).

The Working Group recommends that the Agency solicit additional information on potential teratogenic effects of thiophanate-methyl and exposure from actual use.

Lists of Appendices

1. Clemons, G. P. and H. D. Sisler. 1971. Localization of the site of action of a fungitotoxic benomyl derivative. Pest. Biochem. Physiol. 1:32–43.

2. Vonk, J. W. and A. K. Sijpesteijn. 1971. Methyl benzimidazol-2-ylearbamate, the fungitoxic principle of thiophate methyl. Pest. Sci. 2:160–164.

3. Fleeker, J. R., H. M. Lacy, I. R. Schultz and E. C. Houkorn. 1974. Persistence and metabolism of thiophanate-methyl in soil. J. Agr. Food Chem. 22 (4): 592–595.

4. Noguchi, T. Ohkuma, and S. Kosaka. Cited in *1974 Evaluations of Some Pesticide Residues in Food.* WHO Pesticide Residues Series No. 3. World Health Organization. Geneva. pp. 409–439.

5. Fujino, A., N., Ohkuma, ST. Mou, T. Tanoue, and H. Kamimura. Cited in *1974 Evaluations of Some Pesticide Residues in Food.* WHO Pesticide Residues Series No. 3. World Health Organization. Geneva. pp. 410.

6. Kosaka, S., A. Fujino, T. Tanove and B. Mitsui. Cited in *1976 Evaluations of Some Pesticide Residues in Food.* WHO Pesticide Residues Series No. 5. World Health Organization. Geneva. pp. 375.

7. Buchenauer, H., L. V. Edgington, and F. Grossmann. 1973. Photochemical transformation of thiophanate-methyl and thiophanate to alkyl benzimidazol-2-yl carbamates. Pest. Sci. 5:343–348.

8. *Evaluations of Some Pesticide Residues in Food.* 1974. WHO Pesticide Residues Series, No. 3. World Health Organization. Geneva. pp. 409–439.

9. Saito, E. September 20, 1977. Production data for thiophanate-methyl. Memorandum to the files. Confidential.

10. Styles, J. A. and R. Garner. 1974. Benzimidazolecarbamate methyl ester-evaluation of its effects *in vivo* and *in vitro*. Mutat. Res. 26:177–187.

11. De Brabander, M., R. Van de Veire, F. Aerts, S. Geuens, and J. Hoebeke. 1976. A new culture model facilitating rapid quantitative testing of mitotic spindle inhibition in mammalian cells. J. Nat. Cancer Inst. 56(2):357–363.

12. Seiler, J. P. 1976. The mutagenicity of benzimidazole and benzimidazole derivatives. VI. Cytogenetic effects of benzimidazole derivatives in the bone marrow of the mouse and the Chinese hamster. Mutat. Res. 40: 339–348.

13. Makita, T., Y. Hashimoto and T. Noguchi. 1973. Mutagenic, cytogenetic and teratogenic studies on thiophanate-methyl. Toxicol. Appl. Pharmacol. 24:206–215.

14. Hammerschlag, R. S. and H. D. Sisler. 1973. Benomyl and methyl-2-benzimidazole-

carbamate (MBC): Biochemical, cytological and chemical aspects of toxicity to *Ustilago maydis* and *Saccharomyces cerevesiae*. Pest. Biochem. Physiol. 3:42–54.

15. Richmond, D. V. and A. Phillips. 1975. The effect of benomyl and carbendazim on mitosis in hyphae of *Botrytis cinerea* Pers. ex FR. and roots of *Allium cepa* L. Pest. Biochem. Physiol. 5:367–379.

16. Davidse, L. C. 1973. Antimitotic activity of methyl benzimidazol-2-yl carbamate (MBC) in *Aspergillus nidulans*. Pest. Biochem. Physiol. 3:317–325.

17. Seiler, J. P. 1972. The mutagenicity of benzimidazole and benzimidazole derivatives. I. Forward and reverse mutations in *Salmonella typhimurium* caused by benzimidazole and some of its derivatives. Mutat. Res. 15: 273–276.

18. Kappas, A., M. H. L. Green, B. A. Bridges, A. M. Rogers, and W. J. Muriel. 1976. Bemnomyl—a novel type of base analogue mutagen? Mutat. Res. 40:379–382.

19. Seiler, J. P. 1973. The mutagenicity of benzimidazole and benzimidazole derivatives. II. Incorporation of benzimidazole into the nucleic acids of *Escherichia coli*. Mutat. Res. 17:21–25.

20. Seiler, J. P. 1975. The molecular mechanisms of benzimidazole mutagenicity: *In vitro* studies on transcription and translation. Biochem. Genet. 13 (9/10):635–641.

21. Ficsor, G. and S. Bordas. Mutagenicity tests of benomyl and benomyl-containing products *in vitro* and in rodent host mediated assays in *Salmonella typhimurium*. Department of Biology. Western Michigan University, Kalamazoo. Unpublished.

22. Kappas, A., S. G. Georgopoulos, and A. C. Hastie. 1974. On the genetic activity of benzimidazole and thiophanate fungicides on diploid *Aspergillus nidulans*. Mutat. Res. 26(1):17–27.

23. Stringer, A. and M. A. Wright. 1973. The effect of benomyl and some related compounds on *Lumbricus terrestris* and other earthworms. Pest. Sci. 4:165–170.

24. Stringer, A. and C. H. Lyons. 1974. The effect of benomyl and thiophanate-methyl on earthworm populations in apple orchards. Pest. Sci. 5:189–195.

25. Hopp, H., 1973. *What Every Gardner Should Know About Earthworms*. Garden Way Publishing Co., Charlotte, Vt., 05445. pp. 1–39.

26. Elespuru, R. K. and W. Lijinsky. 1973. The formation of carcinogenic nitroso compounds from nitrite and some types of agricultural chemicals. Food Cosmet. Toxicol. 11:807–817.

27. Wolff, I. A. and A. E. Wasserman. 1972. Nitrates, nitrites and nitrosamines. Science 177(4043):15–19.

28. Borzsonyi, M. and M. Czik. 1975. Induction of malignant lymphomas in Swiss mice by N-nitroso compounds formed *in vivo*. Int. J. Cancer 15:830–838.

29. Borzsonyi, M. A. Pinter, A. Surjan, and I. Farkas. 1976. Transplacental induction of lymphomas in Swiss mice by carbendazim and sodium nitrite. Int. J. Cancer 17:742–747.

30. Baron, R. L. April 18, 1977. Evaluation report to Esther Saito, Project Manager, OSPR. 2 pp.

31. Mittelman, A. April 19, 1977. N-Nitroso benomyl review. Memorandum to Richard Troast, Project Manager, OSPR. With attachments. 25 pp.

32. Freudenthal, R. I. and A. P. Leber. 1977. Report on the validation of studies on benomyl teratogenicity and embryotoxicity in experimental animals. Battelle Laboratories. Columbus, Ohio. Unpublished.

33. Palmer, A. K., M. R. Lavell and A. J. Newman. 1972. Effect of thiophanate methyl on reproductive function of multiple generations in the rat. Submitted to EPA by Pennwalt Corp. on September 7, 1972. EPA Accession No. 091779.

34. Noguchi, T., S. Kosaka, K. Ohkuma, H. Kamimura, Y. Soeda, Y. Hashimoto, T. Mori, N. Ohnuma, and M. Hattori. 1971. Studies on the biotransformation of thiophanatemethyl in animal and plant (Part III) Submitted to EPA by Pennwalt Corp. on February 17, 1972. EPA Accession No. 127270.

**** PRODUCT SEARCH LISTING **** PAGE 1

10/12/77 FEDERALLY REGISTERED PRODUCTS CONTAINING THIOPHANATE-METHYL

REGISTRANT	*NAME AND ADDRESS*
* 000359	RHODIA INC. AGRICULTURAL DIVISION P.O. BOX 125 MONMOUTH JUNCTION, NJ 08852

********** PRODUCT NAME **********

**00665* CHIPCO SPOT KLEEN TURF FUNGICIDE

REGISTRANT	*NAME AND ADDRESS*
* 000372	MALLINCKRODT INC SECOND AND MALLINCKRODT STREETS ST LOUIS, MO 63160

********** PRODUCT NAME **********

**00045* FUNGO 50 SYSTEMIC TURF FUNGICIDE

**00046* BANKUT

REGISTRANT	*NAME AND ADDRESS*
* 000538	SCOTT O M & SONS COMPANY MARYSVILLE OH 43040

********** PRODUCT NAME **********

**00088* PROTURF SYSTEMIC FUNGICIDE

**** PRODUCT SEARCH LISTING **** PAGE 2

10/12/77 FEDERALLY REGISTERED PRODUCTS CONTAINING THIOPHANATE-METHYL

REGISTRANT	*NAME AND ADDRESS*
* 004581	PENNWALT CORP AGCHEM DIV. PENNWALT TECHNOLOGICAL CENTER P.O. BOX C KING OF PRUSSIA, PA 19406

********** PRODUCT NAME **********

**00280* PENNWALT TOPSIN M TECHNICAL

**00288* TOPSIN M 70% WETTABLE POWDER TURF FUNGICIDE ORNAMENTAL TURF USE ONLY

**** PRODUCT SEARCH LISTING **** PAGE 1

10/12/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING THIOPHANATE-METHYL

****

REGISTRANT *NAME AND ADDRESS*

* 000538 SCOTT O M & SONS COMPANY
MARYSVILLE OH 43040

********** PRODUCT NAME **********

OURGG PROTURF FERTILIZER PLUS SYSTEMIC FUNGICIDE

**** PRODUCT SEARCH LISTING **** PAGE 2

10/12/77 APPLICANTS FOR REGISTRATION OF PRODUCTS CONTAINING THIOPHANATE-METHYL

****

REGISTRANT *NAME AND ADDRESS*

* 004581 PENNWALT CORP AGCHEM DIV.
PENNWALT TECHNOLOGICAL CENTER
P.O. BOX C
KING OF PRUSSIA, PA 19406

********** PRODUCT NAME **********

00GLE TOPSIN M THIOPHANATE-METHYL FUNGICIDE, 70% WETTABLE POWDER

[FR Doc.77-34224 Filed 12-6-77;8:45 am]

Advance Orders are now being Accepted
for delivery in about 6 weeks

CODE OF FEDERAL REGULATIONS

(Revised as of July 1, 1977)

Quantity	Volume	Price	Amount
_____	Title 33—Navigation and Navigable Waters (Parts 1–199)	$7.00	$_____
_____	Title 40—Protection of Environment (Part 400–end)	5.75	_____
		Total Order	$_____

[A Cumulative checklist of CFR issuances for 1977 appears in the first issue of the Federal Register each month under Title 1]

PLEASE DO NOT DETACH

MAIL ORDER FORM To:

Superintendent of Documents, Government Printing Office, Washington, D.C. 20402

Enclosed find $..... (check or money order) or charge to my Deposit Account No. .....

Please send me ..... copies of:

PLEASE FILL IN MAILING LABEL BELOW

Name .....

Street address .....

City and State ..... ZIP Code .....

FOR USE OF SUPT. DOCS.

____Enclosed_____

To be mailed later_____

____Subscription_____

Refund_____

Postage_____

Foreign Handling_____

FOR PROMPT SHIPMENT, PLEASE PRINT OR TYPE ADDRESS ON LABEL BELOW, INCLUDING YOUR ZIP CODE

SUPERINTENDENT OF DOCUMENTS
U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON, D.C. 20402

OFFICIAL BUSINESS

POSTAGE AND FEES PAID
U.S. GOVERNMENT PRINTING OFFICE
375
SPECIAL FOURTH-CLASS RATE BOOK

Name .....

Street address .....

City and State ..... ZIP Code .....